REMARKS

Claims 1, 6-8 are pending. Claim 1 was amended and new claim 25 was added in the amendment filed with the RCE on August 16, 2004. Claim 1 is amended and new claims 26-30 are added in this Supplementary Amendment. Support for the new claims can be found, for example, in the specification at page 8, lines 20-23; page 10, lines 6-10 (discussed further below).

Reconsideration of this application is respectfully requested.

Examiner Interview

The undersigned agent wishes to thank Examiner Ly and Examiner Marschel for the courtesies extended to the applicants (Dr. Greene and Dr. Murali) and the applicants' representatives the undersigned and Peter Ludwig at the interview conducted at the USPTO on September 22, 2004. During the interview the invention was explained to the Examiners and the issues raised in the Official Action of March 14, 2004 (the enablement rejection under 35 U.S.C. §112 and the prior art rejection over the "Li" reference under 35 U.S.C. §102) were also discussed.

At the outset of the interview, Dr. Greene explained that the invention involved a method for identifying drug candidates by taking advantage of the allosteric modulation that occurs when a compound binds within a cavity on the target protein that is located a measurable distance away from a functionally critical site (e.g., a ligand binding site on a receptor, or an active site of an enzyme) on the target protein. Binding of the compound to the cavity causes allosteric modulation (e.g., distortion of the three dimensional shape of the target protein). As a result of this three dimensional distortion (allosteric change), the interaction that normally occurs at the functionally critical site may be inhibited. Thus, in the usual situation, a compound or ligand which normally binds to a protein at the functionally critical site (e.g., the ligand binding site of a receptor) and invokes biological response of interest (e.g., signal transduction from the receptor or dimerization of the receptor with another receptor) would be prevented from even binding to the functionally critical site because the geometry of the receptor had been allosterically altered in a manner that rendered the functionally critical site inaccessible for binding to the compound.

Dr. Greene contrasted this with the customary method for inhibiting binding to a functionally critical site by placing an inhibitor directly at the functionally critical site thereby permitting the inhibitor to physically impede binding of an activating compound to the receptor site (i.e., competitive inhibition). Dr. Greene pointed out that this was entirely different from the present invention, which does not inhibit the function of the critical site by interposing a physical barrier, but rather, alters the geometry of the critical site due to allosteric modification of the protein structure. Thus, in the present invention, interaction at a functionally critical site is disrupted by the binding of a distinct compound at a distant site (the allosteric cavity).

Dr. Greene pointed out that the functionally critical site on the target protein could be determined using a 3D model of the protein, and that such a model could be prepared using various techniques including e.g., crystallography, NMR, homology modeling and computer simulation using standard software such as Insight II and Quanta (reference specification page 11 lines 30-31). Once the 3D model of the protein is available, the allosteric cavity (to which the modulating compound is targeted) is identified using e.g., off-the-shelf software such as MS, or Insight II (commercially available from Accelrys Inc.). Once an allosteric cavity is identified, dimensions of the cavity and its chemical and/or electrostatic properties are mapped (using the same software e.g., Insight II or MS). Using the information obtained by mapping, compounds containing functional groups that could be accommodated by the cavity (i.e., bind in the cavity) are identified and such compounds are tested in an *in vitro* assay to determine if they cause an allosteric modification of the intermolecular interaction at the functionally critical site (on the target protein).

Dr. Greene explained that the technology used to prepare a 3-dimensional (3D) model of a protein (e.g., the protein on which the functionally critical site is located) and to map the protein's surface and the cavity was well known at the time the invention was made and widely used in commercial and research laboratories.

Dr. Greene distinguished the present invention from the Li reference, pointing out that Li teaches a method for identifying compounds that bind to a functionally critical site (an epitope) on

the surface of CD4. Li identifies this binding site as the location at which the CD4 receptor interacts (binds) with the MHC II antigen on the antigen presenting cell (see Li at page 74 column 1). Li disrupts the CD4-MHC interaction by competitive binding. That is to say, the compound binds in the functionally critical site and physically interferes with binding between the natural ligand and the receptor. Thus, Dr. Greene said that Li operated by physically blocking interaction between the receptor and the compound that customarily binds at the receptor site, whereas the present invention prevents interaction between the compound that normally binds to a functionally critical site (e.g., the ligand-binding site on the receptor) by e.g., changing the geometry of this site so that it can not receive the binding compound.

The claims were discussed with Examiner Ly and Examiner Marschel. Examiner Marschel suggested that consideration be given to changing the term "a functionally critical site" to " any functionally critical site" based on Dr. Greene's indication that the invention could work with any functionally critical site on the protein. However, after further consideration, it is not believed that this change is required or desirable because, while the invention can be used to identify a compound that modulates any functionally critical site on a target protein, it is in fact used in an effort to locate a compound that modulates a particular (specific) functionally critical site on a target protein. That is to say, in practicing method of the invention, the user is seeking a candidate compound that can be used to inhibit a known function of a particular site on the target protein (e.g., inhibition of binding of the TNF-α ligand to the TNF receptor). Thus, it is submitted that the term " a functionally critical site" is an accurate characterization of the site that is employed in practicing the method of the invention.

However, it is emphasized that the invention requires that the allosteric cavity be distant from the functionally critical site, since the two sites cannot overlap and are mutually exclusive. In other words, one cavity on a target protein cannot be both a functionally critical site and an allosteric site to modulate its own function. For example, for the TNF receptor, the functionally critical site is the point of interaction between a TNF such as TNF-α. This site cannot also be the allosteric site to modulate the binding between TNF and TNF-α.

Examiner Marschel also suggested describing the cavity as employed in practicing the invention as an allosteric cavity. This suggestion has been adopted in the amended claim 1, and in new claims 26-29 (which are variations of claim 1 for the Examiner's consideration).

Support for the new claims can be found in the specification (published PCT WO 00/01349) at page 8, lines 20-23, which states that the functionally critical site refers to a region or location or secondary structural element on a target protein that is involved in either altering or mediating function, *the modulation of which is desirable* (emphasis supplied). Thus, it is presumed that before one can allosterically modulate function, the function to be modulated must be predetermined (i.e., known and of interest to the skilled artisan to modulate). Further support for the new claims is found at page 10, lines 6-10, which states that "Since the interaction with modifiers is necessary for a specific biological function attributed to the target protein, inhibition of the target protein:modifier interaction inhibits the *biological function associated with such interaction*" (emphasis supplied).

At the conclusion of the interview, Examiner Ly indicated that he would withdraw the enablement rejection and would likely withdraw the prior art rejection based on the Li reference after further consideration.

Based on the Examiner's suggestions at the interview, claim 1 has been amended to further clarify the method of the invention and the manner in which it is practiced. New claims have been added as alternatives to claim 1. The amended and new claims are fully supported in the specification and are believed to be in condition for allowance. Should the Examiner find claims 26-30 allowable in lieu of claim 1 the pending claims depending from claim 1 will be amended to depend from the allowable claim.

This application is now believed to be in condition for allowance and such action is earnestly solicited.

Respectfully submitted,

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